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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,453	07/11/2003	Avshalom Caspi	960296.99497	5194

7590 07/17/2006

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,453	CASPI ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *14-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-13 in the reply filed on 4/21/06 is acknowledged. The traversal is on the ground(s) that the overlap between the two is so close that both should be searched and examined together. This is not found persuasive because it would pose as serious burden on the examiner to search and examine both inventions because, a search for the inventions of the two groups would not be coextensive because a search indicating the process is novel or unobvious would not extend to a holding that the products themselves are novel or unobvious; similarly, a search indicating that the product is known or would have been obvious would not extent to a holding that the process is known or would have been obvious. In this case, some of the claims have some overlapping limitations, but not sufficiently so as to eliminate the need for different searches to examine the products of group III and the methods of group I. Therefore, restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 1, 2, 3, 4, 5, 6, 7, 8, 12, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Caspi et al. (Science Volume 297, 2 August 2002, pages 851-854, and including supplemental material pages 1-7).

Caspi et al. teach that a functional polymorphism in the gene encoding the enzyme monoamine oxidase A moderates the effect of maltreatment on children, such that maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems (throughout; summarized in Abstract). Caspi et al. teach a method comprising the steps of determining whether a subject carries one or more copies of an at-risk allele, determining whether the subject has experienced the environmental risk factor of maltreatment, and concluding the subject is predisposed to the phenotype if the subject carries the at risk allele and has experienced the environmental risk factor.

Namely, Caspi et al. teach a method wherein DNA from subjects was extracted and genotyped for alleles of a polymorphism in the allele present of a variable number tandem repeat polymorphism within the promoter of the MAOA gene (p. 852, 1st column; supplemental information, p. 1). Further, Caspi et al. teach a method wherein the subjects were assessed for an environmental risk factor of maltreatment by parents during childhood (p. 852, 1st column; supplemental information, p. 2). Caspi et al. conclude that a the phenotype of antisocial problems is related to the at-risk allele and the environmental risk factor (throughout; Abstract, and Figure 2).

Regarding claim 2, many of the tested subjects carry the at risk allele (Figure 2, for example).

Regarding claim 3, many of the subjects have experienced the environmental risk factor of childhood maltreatment (Figure 2).

Regarding claims 4, 5 and 8, the mental disorder phenotype is a behavioral disorder phenotype, namely antisocial behavior, and the genetic variation in this tested population had an

attributable risk faction of 11%, which is a high proportion of total phenotypic population variation.

Regarding claims 6, 7, and 8, the pathogenic environmental risk factor is exposure to psychosocial stress, namely, maltreatment by parents (Figure 2).

Regarding claim 12, Caspi et al. teach amplifying a portion of the gene using a primer pair and determining the length of the amplified fragment, which inherently determines whether the amplified fragment is a fragment of the at-risk allele (supplement, page 1), and regarding claim 13, Caspi et al. teach using amplification primers having a sequence of SEQ ID NO: 1 and SEQ ID NO: 2.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of assessing a human subject for a predisposition to conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior, the method comprising the steps of

determining whether the subject carries a two or three repeat allele of a variable number tandem repeat polymorphism within the gene encoding human monoamine oxidase A enzyme, wherein the locus of said promoter is amplified using instant SEQ ID NO: 1 and SEQ ID NO: 2,

determining whether the subject has experienced childhood maltreatment, and

concluding that the subject is predisposed to conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior, if the subject carries the a two or three repeat allele and if the subject has experienced the environmental risk factor, does not reasonably provide enablement for methods for predicting predisposition in non-humans, methods which consider associations between other polymorphisms within MAOA or polymorphisms in other genes that may be linked to expression of MAOA and these or other phenotypes, methods which predict predisposition to additional phenotypes, or methods which relate other environmental risk factors to these or additional phenotypes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to a method for assessing predisposition of disorder phenotypes in any possible subject, human or non-human.

The instant claims are further broadly drawn to assessing a predisposition to any "mental disorder phenotype having an association with an at risk allele of a gene that encodes monoamine oxidase A enzyme, the association being conditioned by a pathogenic environmental risk factor status condition" a group of possible disorders which the specification teaches includes juvenile conduct disorder, antisocial personality disorder, psychosis, depression, anxiety, dementia, reading disability (¶ 0015 and ¶0016), but is also sufficiently broad to include any other possible disorder phenotype that is a behavorial, emotional or cognitive disorder, including learning delays, alcoholism, bipolar disorder, and a variety of additional phenotyes that are not joined by any particular cause, symptom or eteiology, but are all "mental disorder

phenotypes" of one type or another. The specification provides no guidance as to which of these particular phenotypes, other than conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior, might have an association with an "at risk" allele of the MAOA gene where that association is conditioned by a pathogenic environmental risk.

Further, the scope of the "pathogenic environmental risk" set forth in the claims is extremely broad, including any possible pathogenic environmental risk, including, for example, childhood maltreatment, psychological trauma, psychosocial stress, unhealthy diet, infectious agents, toxic agents pharmacological agents, medical trauma and injury, as set forth in claims 6 and 7. Even these particularly listed risks are themselves broad, for example, medical trauma could include heart attacks, stab wounds, burst appendix, and a wide variety of other possible traumas.

The claims are broad with regard to the nature and identity of the "as-risk allele" of a gene that encodes MAOA enzyme, providing only the functional requirement that it is characterized by a low activity level of the enzyme. Such an allele could include truncations, deletions, substitutions, repeats, and any other possible genetic alterations.

Thus, the scope of the claims is quite broad. The nature of the invention requires the knowledge of an association between an allele of the MAOA enzyme gene an a particular phenotype, wherein that association is conditioned by a risk factor, in order to predict a predisposition to that phenotype. The claims specifically require that the mental disorder phenotype whose predisposition is assessed has an association with an at risk allele such that the association is "conditioned" by a pathogenic environmental risk factor status condition.

The specification does not provide any working examples where the method of the claimed invention is actually practiced, that is, where the method is used to assess the predisposition of an individual. The specification, however, exemplifies a relationship between one possible environmental risk factor, namely childhood maltreatment in males, and the mental disorder phenotypes conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior (see pages 11-16 of the specification). These pages of the specification focus exclusively on a relationship that involves the examination of a single polymorphic location, that is a polymorphism variable number tandem repeat polymorphism that is known to effect expression. The specification does not provide the identity of any additional polymorphisms that are known to effect expression of this gene or that are associated with the studied mental disorder phenotypes, in humans or in other animals. The specification does not provide any data or guidance as to the relationship between the polymorphism studied and additional mental disorder phenotypes or risk factors.

There is a high degree of unpredictibilty regarding the association of polymorphisms within the MAOA enzyme encoding gene and mental disorder phenotypes. The state of the prior art does not provide any data or evidence regarding another association that is "conditioned" by a particular risk factor. The prior art does however demonstrate many instances where practitioners attempted to establish relationships between polymorphisms within MAOA and mental disorder phenotypes and failed. For example, Wei et al. teach that they observed no significant differences in frequency of alleles a microsatellite repeat in MAOA between controls and subjects with schizophrenia (Wei et al. Eur Psychiatry 1998, Vol. 13, pages 407-410). Hamilton et al. (Molecular Psychiatry, 2000, Vol. 5, pages 465-466) teach that they found no

genetic linkage or association between a polymorphism in the MAOA promoter and panic disorder. Norton et al. studied a single nucleotide polymorphism and a VNTR polymorphism in the MAOA gene and found no evidence for association with schizophrenia (Norton et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2002,114:491-496). Additional attempts were made to associate genotypes of the MAOA gene with completed suicides, manic-depressive illness, bipolar disorder, and unipolar disorder, but these were unsuccessful (Ono et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2002, 114:340-342; Parsian et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 1997, 74:475-479; and Kungi et al. Molecular Psychiatry, 1999, Vol. 4, 393-395). These studies together exemplify the high degree of unpredictability in this subject area. The lack of guidance in the specification regarding the application of the claimed methods using additional genotypes with MAOA to different phenotypes with different risk factors is particularly difficult to overcome in view of such a high degree of unpredictability in the prior art.

Thus, having carefully considered all of these factors, it is concluded that the specification is not sufficient to enable one to make and use the invention commensurate in scope with the instant claims.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30

PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

July 10, 2006